readable form (CRF). The CRF and the paper listing are identical. The sequence listing in this amendment differs from the listing as filed only by the addition of the sequences listed on page 33 of the specification. This submission therefore, does not contain new matter.

Respectfully submitted,

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Aβ1-40, whereas expression of wild-type PS1 or SEL-10 has no effect on the ratio of Aβ1-42/total Aβ [1,2].

The genetic data indicates that SEL-10 is a negative regulator of presenilin activity in *C. elegans*. Loss of SEL-10 function presumably rescues the egg laying defect in *sel-12* mutant worms through facilitation of HOP-1 presenilin activity, perhaps by allowing the increased accumulation of processed N- and C-terminal fragments of HOP-1. *Sel-10* was identified in a screen for mutations that increase presenilin activity [11]. In principle, genetic screens in model organisms such as *C. elegans* or *Drosophila* can be used to find mutations that decrease presenilin activity, the desired therapeutic goal in Alzheimer's disease [26]. Such screens have the potential to identify novel therapeutic targets for this devastating disease.

Methods

Cloning. Incyte clone (028971) was identified as the human homologue of C. elegans *sel-10* and its sequence was used to design four antisense oligonucleotide primers 5'-TCACT-TCATGTCCACATCAAAGTCC-3' (SEQ ID NO: 28), 5'-GGTAATTACAAAGTTCTTG-TTGAACTG-3' (SEQ ID NO: 29), 5'-CCCTGCAACGTGTGTAGACAGG-3' (SEQ ID NO: 30), and 5'-CCAGTCTCTGCATTCCACACTTTG-3' (SEQ ID NO: 31), to amplify the remainder of the human *sel-10* sequence. "Electronic Northern" analysis revealed expression of *sel-10* in hippocampus and mammary gland so these tissues were chosen for 5'RACE cloning using Marathon kit (CloneTech). Marathon-ready cDNA from hippocampus and mammary gland were prepared as directed in the kit. PCR products were cloned into the TA vector pCR3.1 (Invitrogen), and isolates were sequenced. An alternate 5' oligonucleotide primer was also designed based on Incyte clones that have 5' ends that differ from the hippocampal sel-10 sequence (5'-CTCAGACAGGTCAGGACATTTGG-3' (SEQ ID NO: 32). Blastn was used to search the Incyte databases LifeSeq and LifeSeqFL. Gap alignments and translations were performed with GCG programs.

Plasmids and transfections. The human *sel-10* cDNA was inserted into the EcoR1 site of the vector pCS2+MT (gift of Jan Kitajewski, Columbia University College of Physicians and Surgeons). This fused a 5' 6-myc epitope tag in- frame to the fifth methionine of the hippocampal *sel-10* cDNA. The hippocampal and mammary *sel-10* cDNA diverge upstream of this methionine. A PS1 cDNA with a 3'-FLAG tag (PS1-C-FLAG) was inserted into the